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Our Ref: 423005/JGS

P/00/008

Section 29(1)

Regulation 3.1(2)

AUSTRALIA

Patents Act 1990

NOTICE OF ENTITLEMENT

We, CIBA-GEIGY AG of Klybeckstrasse 141, CH-4002 Basle, Switzerland and JAGO PHARMA AG of Eptingerstrasse 51, 4132 Muttenz, Switzerland, the applicant in respect of Application No. 12188/92 state the following:-

1. CIBA-GEIGY AG and JAGO PHARMA AG are the Nominated Persons in respect of the application.

2. The actual inventors of the invention, the subject of the application, are Manfred Keller and Kurt Herzog.

3. The Nominated Person, CIBA-GEIGY AG is entitled to the grant of a patent in respect of the application because the said CIBA-GEIGY AG derived title to the invention from the said actual inventors by Assignment. The Nominated Person, Jago Pharma AG, is entitled to the grant of a patent in respect of the application because the said Jago Pharma AG is the assignee of a part interest in the invention from Ciba-Geigy AG.

4. The Nominated Persons are entitled to claim priority from the basic application listed on the patent application form because (i) the Nominated Person CIBA-GEIGY AG is the Applicant in respect of the basic application and (ii) the basic application was the first application made in a convention country in respect of the invention the subject of the application.

DATED this 12th day of May, 1993.

CIBA-GEIGY AG and JAGO PHARMA AG
By Its Patent Attorneys
DAVIES COLLISON CAVE

J. G. SIELY FIPAA

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Our Ref: 423005

P/00/001
Section 29

AUSTRALIA

Patents Act 1990

PATENT REQUEST : STANDARD PATENT

I/We, being the person/s identified below as the Applicant, request the grant of a patent to the person/s indicated below as the Nominated Person/s, for an invention described in the accompanying standard complete specification.

Full application details follow.

[71] [70] Applicant/s and Nominated Person/s:
Ciba-Geigy AG,
of Klybeckstrasse 141, 4002 BASLE, SWITZERLAND,
Jago Pharma AG,
of Eptingerstrasse 51, 4132 MUTTENZ, SWITZERLAND

[54] Invention Title:
Pharmaceutical aerosol formulations

[72] Name/s of actual inventor/s: (optional)
Manfred KELLER; Kurt HERZOG

[74] Address for service in Australia:
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Attorney Code : CA

BASIC CONVENTION APPLICATION/S DETAILS:

[31] Appln No.:	[33] Country:	Code:	[32] Date:
781/91-2	SWITZERLAND	CH	14 March 1991

DATED this TENTH day of MARCH 1992

Ciba-Geigy AG, Jago Pharma AG
By Patent Attorneys
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Hector Cumming

HECTOR CUMMING, FIPAA

Fee: $ 208.00

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PHARMACEUTICAL AEROSOL FORMULATIONS

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(56) Prior Art Documents
US 4174295
EP 372777
US 5118494

(57) Claim

1. A pharmaceutical composition for use as an aerosol comprising:
a) a liquefied propellant gas or propellant gas mixture having a vapour pressure of more than 1 bar and less than 6 bar (20°C) from the group consisting of unsubstituted hydrocarbons and partially to completely fluorinated hydrocarbons;
b) a non-ionic surfactant from the group consisting of monoacetylated or diacetylated monoglycerides;
c) a pharmaceutical active ingredient or active ingredient combination and, optionally,
d) other conventional pharmaceutical excipients that are suitable for aerosol formulations.

5. A process for the preparation of the pharmaceutical composition according to claim 1 which comprises placing the pharmaceutical active ingredient or active ingredient combination c) in a pressure-tight vessel and introducing, in any desired sequence of the steps, the non-ionic surfactant b), where appropriate the conventional pharmaceutical excipients d), and introducing the propellant gas or propellant gas mixture a), homogenising, and introducing the homogeneous mixture into dosing vessels suitable for aerosol formulations.

8. The use of a non-ionic surfactant from the group of the monoacetylated or diacetylated monoglycerides for the preparation of a pharmaceutical composition that can be used as an aerosol formulation.

Our Ref: 423005

P/00/011
Regulation 3:2

AUSTRALIA

Patents Act 1990

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ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT

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Invention Title: Pharmaceutical aerosol formulations

The following statement is a full description of this invention, including the best method of performing it known to me:-

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4-18582/A

Pharmaceutical Aerosol Formulations

The invention relates to a pharmaceutical composition comprising chlorine-free propellant gases for use as an aerosol formulation, to a process for the preparation of that pharmaceutical composition and to its use in a method of therapy, especially in inhalation therapy.

The administration of active ingredients using aerosols is becoming increasingly important, especially using inhalation dosing aerosols, for the treatment of disorders of the respiratory tract, for example asthma or allergic rhinitis (hay fever). By means of such an aerosol the active ingredient is able to reach the actual target site, for example the bronchioles, in an effective dose without burdening the entire organism to the extent that occurs, for example, with peroral administration.

An aerosol is a mixture of substances consisting of a gaseous dispersant and liquid or solid, disperse constituents (ABC Chemie, vol. 1, page 23, 2nd edition 1974, Verlag Harri Deutsch, D-6000 Frankfurt/Main).

The gaseous dispersant is called propellant gas, and may also consist of a mixture of several propellant gases. For pharmaceutical applications, the disperse constituents consist of liquid or solid active ingredients, a distinction being made between powder or suspension aerosols (solid/gaseous) and emulsion or liquid aerosols (liquid/gaseous). Aerosols may additionally comprise other excipients, such as surfactants.

The term "aerosols" is used especially for mixtures of substances in pressure-tight vessels (spray cans) that contain the gaseous dispersant under pressure in the liquid state at room temperature. The pressure-tight vessels are closed by a metering or pressure valve. Upon administration after operating the metering valve, the actual aerosol, comprising solid particles or droplets dispersed in the propellant gas, escapes from the pressurised vessel.

Discussions and investigations concerning the cause of damage to the atmospheric ozone layer by chlorofluorocarbons (CFCs) have limited the industrial use as propellant gases in

spray cans by regulations of the legislature in many countries. It is known from various research works that only the chlorine atoms in the CFCs and the reactive radicals resulting therefrom are responsible for the damage to the ozone layer.

For industrial, non-pharmaceutical applications, therefore, so-called alternative propellant gases or propellants, for example saturated hydrocarbons, such as propane or n-butane, or chlorine-free fluorohydrocarbons (HFCs or FCs), for example tetrafluoroethane, or mixtures of those propellant gases are increasingly being used. From the ecological standpoint alone there is an urgent need to replace also for pharmaceutical applications all CFCs, which are potentially damaging to the ozone layer, by environmentally more acceptable, alternative propellant gases.

Suitable propellant gases for pharmaceutical applications and also suitable propellant gases or propellants for pharmaceutical aerosols are those that can be liquefied under pressure at room temperature and that are toxicologically safe and do not exhibit side-effects upon inhalation or topical administration.

For inhalation therapy in particular, there is a need for aerosols in which the solid particles or droplets dispersed in the propellant gas have a preferred diameter of about 0.5 - 6 µm. It is desirable that suspension aerosols comprise the active ingredient distributed as homogeneously as possible so that, after shaking, it remains in the finely dispersed state for as long as possible. It is also desirable that the particle size distribution remains unchanged caused by solubility effects of the solid active ingredient suspended in the propellant composition.

European Patent Application 372 777 discloses aerosol formulations comprising the "alternative" propellant tetrafluoroethane (134a). In order to increase the stability of suspensions in that liquefied propellant, it is proposed that a suspension aid in the form of a non-ionic surfactant, for example a sorbitan fatty acid ester of the SPAN type, for example SPAN 85 (sorbitan trioleate), be used. Owing to the insufficient solubility of such surfactants in the liquefied propellant 134a, a solvent, for example ethanol, that has a higher polarity than does the propellant itself is added.

The problem underlying the present invention is to determine a specific suspension aid for active ingredients in aerosol formulations that dissolves more readily in liquefied "alternative" propellant gases than do the known suspension aids hitherto used for that

purpose. In solving this problem, it has surprisingly been found that non-ionic surfactants from the group consisting of monoacetylated and diacetylated monoglycerides are readily soluble in the "alternative" propellant gases mentioned, especially in heptafluoropropane (227), and promote the production of homogeneous suspensions while additionally exhibiting outstanding lubricating properties for the dosing valve.

The present invention relates to a pharmaceutical composition for use as an aerosol comprising:

a) a liquefied propellant gas or propellant gas mixture having a vapour pressure of more than 1 bar and less than 6 bar (20°C) from the group consisting of unsubstituted hydrocarbons and partially to completely fluorinated hydrocarbons;
b) a non-ionic surfactant from the group consisiting of monoacetylated and diacetylated monoglycerides;
c) a pharmaceutical active ingredient or active ingredient combination and, optionally,
d) other conventional pharmaceutical excipients that are suitable for aerosol formulations.

In an especially preferred embodiment of the invention, the aerosol comprises the alternative propellant gas heptafluoropropane (227). This propellant gas has the advantage of a lower vapour pressure of approximately 4 bar compared with the higher vapour pressure of approximately 5.7 bar exhibited at the same temperature by the alternative propellant gas tetrafluoroethane (134a).

The term "pharmaceutical composition" defines a mixture of substances that is suitable for various applications as an aerosol, preferably for inhalation, but also topically, in humans and animals, preferably in humans, and can be used for the treatment of various disorders, for example asthma or allergic rhinitis.

The term "aerosol" is defined hereinbefore. The pressure vessel for producing the aerosol itself may contain the active ingredient or active ingredient combination either in solid form as a suspension or in liquid form as an emulsion or solution in the propellant gas or propellant gas mixture compressed to a liquid. In the technical literature, the pressure vessel together with its contents and the metering valve are occasionally referred to as a dosing aerosol. Within the scope of the description of this invention, the term "dosing aerosol" is intended to refer only to the contents of the pressure vessels.

The propellant gas or propellant gas mixture is so selected that, at a temperature of approximately 20°C, it is in a liquid state of aggregation and has a minimum pressure higher than approximately 1 bar up to a maximum pressure of approximately 6 bar. Suitable propellant gases or propellant gas mixtures are, therefore, those that exhibit a constant internal pressure in the dosing vessel until the latter is completely empty and that, in view of the environmental problems mentioned hereinbefore, do not have any removable chlorine atoms.

Such propellant gases or propellant gas mixtures are known *per se* for the preparation of pharmaceutical aerosols, for example unsubstituted saturated hydrocarbons, for example n-propane, n-butane or isobutane or mixtures thereof, or partially fluorinated or completely fluorinated (perfluorinated) hydrocarbons.

Partially fluorinated hydrocarbons are derived from aliphatic hydrocarbons having preferably from 1 to 4 carbon atoms, for example methane, ethane, propane, n-butane or isobutane, or from cycloaliphatic hydrocarbons having preferably 3 and 4 carbon atoms, for example cyclopropane or cyclobutane, by replacing the hydrogen atom(s) with at least one fluorine atom and preferably at least two fluorine atoms in such a manner that at least one hydrogen atom, and accordingly one hydrocarbon bond, remains in the molecule.

Completely fluorinated (perfluorinated) hydrocarbons are derived from the mentioned aliphatic hydrocarbons having from 1 to 4 carbon atoms and from the mentioned cycloaliphatic hydrocarbons having 3 and 4 carbon atoms by replacement of the hydrogen atoms with corresponding fluorine atoms.

Suitable partially or completely fluorinated hydrocarbons are, for example, methane derivatives having from 1 to 4 fluorine atoms, ethane derivatives having from 1 to 6 fluorine atoms, propane derivatives having from 1 to 8 fluorine atoms, n-butane derivatives having from 1 to 10 fluorine atoms, cyclopropane derivatives having from 1 to 6 fluorine atoms and cyclobutane derivatives having from 1 to 8 fluorine atoms. In these partially or completely fluorinated hydrocarbons, the hydrogen atom or atoms may be located at different places in the hydrocarbon structure. For partially fluorinated hydrocarbons the following cases of isomerism are possible:

If only one hydrogen atom is present, in the propane and butane derivatives it may be terminal or located at an intermediate member of the carbon chain.

If there is more than one hydrogen atom, then still further cases of isomerism are possible for the ethane, propane, n-butane, cyclopropane and cyclobutane derivatives and for hydrocarbons having an even higher number of carbon atoms. Some or all of the hydrogen atoms may be terminal and some or all may be located at one or at different intermediate members of the carbon chains. "Mixed" cases of isomerism are also possible, in which the hydrogen atoms are located, in varying distribution, at the terminal carbon atoms and at the same or at different carbon intermediate members in the case of aliphatic derivatives, or at the same or at different ring carbon members in the case of cycloaliphatic derivatives.

In order to shorten the usual nomenclature and to differentiate the partially fluorinated hydrocarbons mentioned and also the completely fluorinated hydrocarbons mentioned hereinafter, code names are commonly used; these are explained in "Pharmazeutische Technologie", H. Sucker, P. Fuchs, P. Speiser (editor), Thieme Verlag, D-7000 Stuttgart 1978, on page 735 and can also be applied to CFCs. For the numerous cases of isomerism mentioned, suffixes using the letters a, b ... are customary.

Preferred partially fluorinated hydrocarbons are pentafluoroethane (125), tetrafluoroethane (134 and 134a), trifluoroethane (143a), difluoroethane (152 and 152a) and heptafluoropropane (227).

A non-ionic surfactant from the group of the monoacetylated and diacetylated monoglycerides is a monoglyceride (glycerol esterified by a saturated or unsaturated fatty acid) that contains, in addition to the acyl radical of a fatty acid, preferably one or even two acetyl radicals. The acyl radical is preferably derived from an unsaturated fatty acid having more than ten, and an even number of carbon atoms. A monoglyceride that is obtainable from a mixture of monoacetylated or diacetylated monoglycerides using the customary separation methods, for example fractional distillation, is preferred.

The acetylated monoglyceride contains as the acyl radical of a saturated fatty acid, for example a C_{10-20}alkanoyl radical having an even number of carbon atoms, for example n-dodecanoyl, n-tetradecanoyl, n-hexadecanoyl, n-octadecanoyl or n-icosanoyl.

The acetylated monoglyceride contains as the acyl radical of an unsaturated fatty acid preferably a C_{10-20}alkenoyl radical having an even number of carbon atoms, for example

9-cis-dodecenoyl, -tetradecenoyl or -hexadecenoyl, 6-cis- or 6-trans-octadecenoyl, 9-cis- or 9-trans-octadecenoyl or 11-cis-octadecenoyl.

Especially preferred are acetylated monoglycerides that are obtainable commercially under the Trademark MYVACET (Eastman) and authorised by health authorities, e.g. the FDA in the USA, for use as additives for processed foods. Acetylated monoglycerides of the MYVACET series are used as lubricants, plasticisers, non-ionic emulsifiers and solubilisers. The products obtainable commercially under the name MYVACET 5-07, 7-00, 7-07, 9-08, 9-40 and 9-45 are especially preferred.

Most especially suitable are the liquid acetylated monoglycerides, for example MYVACET 9-40 and MYVACET 9-45 K, that can be characterised as follows:

solidification point:	7-8°C
density at 20°C:	0.98-0.99 [g/cm^3]
hydroxyl number:	15
acid number:	3
iodine number:	40-51
saponification value:	370-380

Surprisingly, it has now been found that it is possible to prepare especially homogeneous and stable suspensions using liquid MYVACET types, especially with active ingredients from the group of betasympathomimetics, e.g. salbutamol or formoterol fumarate, in the mentioned alternative liquefied propellant gases or propellant gas mixtures of component a) which do not damage the ozone layer. Surprisingly, it was also found that undesirable adhesion to the wall of the pressure vessel can be prevented by the addition of a polar solvent such as ethanol. Furthermore, it was found that, using the combination MYVACET and ethanol, other active ingredients from chemically different classes of substances also can be converted, together with propellant gases such as 227 or 134a and n-butane, into homogeneous and readily re-dispersible suspensions that can be used as aerosol formulations.

The non-ionic surfactant b) is present in the pharmaceutical composition in a concentration of approximately from 0.0001 to 5.0, preferably approximately from 0.001 to 0.5, % by weight.

In principle, there are suitable for the aerosol formulation all active ingredients or active ingredient combinations c) that are inert towards the propellant gas component a) and component b), the non-ionic surfactant, and to any additional excipients present. The choice of active ingredients is governed by the diagnosis and subject to the limitation of being able to administer the chosen active ingredient or active ingredient combination as an aerosol formulation, preferably by inhalation, but also topically.

Suitable active ingredients are, for example:

Alkaloids: bromocriptine, ergotamine, atropine;
Anti-allergics: azelastin, cetirizin, epinastin, nedocromil, disodium cromoglycate, ketotifen, pemirolast, traxanox, amlexanox, protopine, tepoxalin, midaglizole, picumast, quazolast, repirinast, suplatast;
Antibiotics: fusafungine, gentamycin, neomycin, minocycline, erythromycin, streptomycin, ofloxacin, ciprofloxacin, cephalexin, cefatrizine, cefaclor, ceftriaxone;
Antimycotics: clotrimazole, ketoconazole, amorolfin, bifonazole;
Betasympathomimetics: bambuterol, salbutamol, formoterol, salmeterol, pirbuterol, carbuterol, clenbuterol, reproterol, rimiterol, hexprenaline, fenoterol, bitolterol, terbutaline, mabuterol, tulobuterol;
Anticholinergics: ipratropium, oxitropium, telenzepine, troventol;
Potassium channel openers: cromakalim, lemakalim;
Corticoids: budesonide, flunisolide, beclomethasone, fluticasone, triamcinolone, fluocortinbutyl, butixocort, cloprednol, fluticason, mometason, tipredane;
Mucolytics: acetylcysteine, ambroxole, carbocysteine, furosemide, amiloride;
Phosphodiesterase-inhibitors: theophylline, isbuphylline, zandaverine, enprophylline;
Thromboxane inhibitors, e.g. vapiprost, ozagrel; Leucotriene inhibitors, e.g. bunaprolast, ibudilast;
Platelet aggregation factor(PAF) antagonists, e.g. ginkgolides or mequitamium;
Antiinfective agents: pentamidin, hydroxychloroquine; and
cytostatic agents such as methotrexate.

Especially preferred are active ingredients that are used in inhalation therapy for the prophylactic and/or acute treatment of bronchial obstructions, such as asthma, for example salbutamol, formoterol, salmeterol, disodium cromoglycate, nedocromil, oxitropium, ipratropium, budesonide, beclomethasone, flunisolide and triamcinolone.

If they contain a salt-forming group, the mentioned active ingredients may be present in the aerosol in the form of the free compounds or in the form of their pharmaceutically acceptable salts.

The aerosol comprises the active ingredient or active ingredient combination in a proportion of approximately from 0.0001 to 5.0 % by weight, preferably approximately from 0.001 to 2.5 % by weight.

It is possible to admix with the pharmaceutical composition, for example, customary pharmaceutical excipients that are suitable for aerosol formulations. For example, a solvent having a higher polarity than that of the liquefied propellant gas component a) can be added. Since the propellant gases or propellant gas mixtures of component a) have little polarity, numerous other, more polar solvents, such as ethanol, isopropanol, propylene glycol, dimethyl ether and mixtures of those solvents, which may be added in any desired concentrations, for example from approximately 0.1 to 30 % by weight, are suitable as additives.

As additional excipients there may be added, in addition to component b), other non-ionic surfactants that increase the wetting and dispersibility of pharmaceutical active ingredients still further and/or, as lubricants, improve the mechanical valve functions and prevent the deposition of solids by adsorption onto the inside of the pressure vessel.

Such additional non-ionic surfactants are, for example, sorbitan fatty acid esters, for example sorbitan trioleate, sesquioleate, monooleate or monolaurate, which are commercially obtainable, for example, under the Trademark SPAN, for example SPAN 85, 80 and 20, polyoxyethylenesorbitan esters, for example polyoxyethylene(20)sorbitan monolaurate or monooleate, for example esters that are obtainable commercially under the Trademark TWEEN, for example TWEEN 20, 40, 60 and 80, oleyl, stearyl or lauryl polyoxyethylene esters that are obtainable commercially under the Trademarks BRIJ or GENAPOL, for example BRIJ 92, 72, 30 or GENAPOL 0-020, and block copolymers that are commercially obtainable under the Trademarks SYNPERONIC.

Other excipients are, for example, pharmaceutically approved oils, for example oils of vegetable origin, for example from corn, olives, cotton seeds, rape or sunflowers, phospholipids, for example synthetic lecithin or natural lecithin dervivatives that are commercially obtainable under the Trademark EPIKURON, diethylene glycol dioleate,

tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl trioleate, glyceryl monolaurate, monooleate or monoricinoleate, cetyl alcohol, polyethylene glycol 400, polyol fatty acid esters or cetylpyridinium chloride. Taste correctives, such as saccharin, aspartames and flavourings, for example dentomint, can also be added.

The mentioned excipients of component d) may be added in a proportion of approximately from 0.0001 to 10 % by weight, preferably approximately from 0.001 to 1 % by weight, based on the entire weight of the pharmaceutical formulation.

The present invention relates preferably to a pharmaceutical composition comprising:
a) a propellant gas or propellant gas mixture selected from the group consisting of propane, n-butane, isobutane, di-, tri-, or tetrafluoroethane (134a) and heptafluoropropane (227);
b) a non-ionic surfactant from the group consisting of monoacetylated monoglycerides;
c) a pharmaceutical active ingredient or active ingredient combination from the group consisting of the antiallergics, e.g. disodium cromoglycate or nedocromil, betasympathomimetics, e.g. salbutamol, salmeterol or formoterol, anticholinergics, e.g. oxitropium- or ipratropium bromide, and corticoids, e.g. budesonide, flunisolide, beclomethasone or triamcinolone, and, optionally,
d) further conventional pharmaceutical excipients that are suitable for aerosol formulations.

The present invention relates preferably to a pharmaceutical composition comprising:
a) a propellant gas or propellant gas mixture from the group consisting of propane, n-butane, isobutane, tetrafluoroethane (134a) and heptafluoropropane (227);
b) a non-ionic surfactant from the group consisting of monoacetylated monoglycerides;
c) a pharmaceutical active ingredient or active ingredient combination from the group consisting of disodium cromoglycate, salbutamol, salmeterol, formoterol, oxitropium bromide, ipratropium bromide, budesonide, flunisolide, beclomethasone and triamcinolone, and, optionally,
d) further conventional pharmaceutical excipients that are suitable for aerosol formulations.

The present invention relates especially to a pharmaceutical composition comprising:
a) the propellant gas heptafluoropropane (227);
b) a non-ionic surfactant from the group consisting of monoacetylated monoglycerides;

c) a pharmaceutical active ingredient or active ingredient combination from the group disodium cromoglycate, salbutamol, salmeterol, formoterol, oxitropium bromide, ipratropium bromide, budesonide, flunisolide, beclomethasone and triamcinolone and, optionally,
d) further conventional pharmaceutical excipients that are suitable for aerosol formulations.

The present invention also relates to a process for the preparation of the pharmaceutical composition which is carried out in a manner known *per se* and is described, for example, in the aforementioned "Pharmazeutische Technologie" on pages 736-737.

The pharmaceutical composition can be prepared by placing the pharmaceutical active ingredient or active ingredient combination c) in a pressure-tight vessel and introducing, in any desired sequence of the steps, the non-ionic surfactant b), where appropriate the conventional pharmaceutical excipients d), and introducing the propellant gas or propellant gas mixture a), homogenising, and introducing the homogeneous mixture into dosing vessels suitable for aerosol formulations.

If the active ingredient or ingredients is/are in solid, for example crystalline, form, they are to be comminuted, preferably by micronisation. The upper limit for the average particle size in the case of topical formulations is considered to be an average particle diameter of less than 100 and, in the case of inhalation formulations for the purpose of deposition in the respiratory tract, less than 10 micrometers. A particle size of approximately from 0.1 to 5 micrometers is preferred for inhalation formulations, which can be achieved by the use of conventional comminution methods, for example grinding in an air jet mill.

Component c) is weighed into an open batch pressure vessel equipped with a stirring and homogenising apparatus, and there are added, according to the formulation instructions, in the desired sequence, components b) - surfactant - and, where appropriate, d) other excipients, for example ethanol. The pressure vessel is closed and the propellant gas or propellant gas mixture is introduced. The active ingredient is homogenised in the propellant gas/excipient mixture in the customary manner, for example by stirring, shaking or treatment with ultrasound. Using known filling techniques, the contents of the pressure vessel are introduced through the valve into dosing vessels, for example pressure-tight vessels consisting of tinplate or aluminium which are referred to in common parlance as spray cans and are provided with the customary dosing valves. The pres-

sure-tight valves release approximately from 25 to 100 microlitres in the case of inhalation dosing aerosols.

The invention also relates to the use of the pharmaceutical aerosol composition in a therapeutic method, for which a need exists depending on the therapeutic category of the active ingredient or active ingredient combination present in the claimed composition. The pharmaceutical aerosol composition is especially useful for the treatment by inhalation of allergic diseases of the respiratory tract such as asthma or allergic rhinitis, especially in the event that the composition contains active agents such as formoterol, disodium cromoglycate or salbutamol.

The invention also relates to the use of a non-ionic surfactant from the group of the monoacetylated or diacetylated monoglycerides for the preparation of a pharmaceutical composition that can be used as an aerosol. Especially preferred is the use of a liquid, non-ionic acetylated monoglyceride that is known under the name MYVACET.

The following Examples illustrate the invention:

The active ingredient, micronised to a particle size of less than 6 micrometers, is weighed according to the Recipe into a previously dried batch pressure vessel, and the propellant gas or propellant gas mixture, comprising, in the respective concentrations according to the Recipe Example, the excipient ethanol, the non-ionic surfactant MYVACET and, where appropriate, other excipients, is added. After stirring and homogenising, the pressurised suspension is diluted with propellant gas where appropriate, and introduced by the customary pressure fill technique into aluminium or glass vessels of approximately 20 ml volume which are closed by a dosing valve. In the Recipe Examples, the amounts weighed in are each given in % by weight:

Recipe Example No.	1	2	3	4	5	6	7
formoterol fumarate	0.017	0.017	0.017	0.017	0.017	0.017	0.017
ipratropium bromide			0.086	0.086	0.086		
MYVACET 9-40	0.030	0.030	0.043	0.086	0.0152		
MYVACET 9-45						0.017	0.034
SPAN 85						0.019	
ethanol						5.0	5.0
n-butane		69.953	69.946		69.745		
tetrafluoroethane		30.0	30.0		30.0		
heptafluoropropane	99.953			99.810		94.947	94.949

Recipe Example No.	8	9	10	11	12
formoterol fumarate	0.017	0.017	0.03	0.017	0.03
ipratropium bromide				0.086	0.154
MYVACET 9-40			0.03		
MYVACET 9-45	0.008	0.034		0.017	0.153
SPAN 85					
ethanol	2.6				
n-butane			69.0		
tetrafluoroethane		99.949	30.94		69.7
heptafluoropropane	97.375			99.88	29.963

Recipe Example No.	13	14	15	16	17
salbutamol base	0.143	0.143	0.143		
disodium cromoglycate				1.5	1.5
budesonide					
MYVACET 9-40	0.014	0.014		0.15	0.1
MYVACET 9-45			0.14		
ethanol	5.0	5.0	1.0	5.0	5.0
n-butane		64.843			65.1
tetrafluoroethane		30.0			33.3
heptafluoropropane	94.843		98.843	98.35	

Recipe Example No.	18	19	20	21	22	23
salbutamol base	0.142					
salbutamol sulfate		0.142				
disodium cromoglycate				1.587		
ipratropium bromide			0.029			
beclomethasone dipropionate					0.367	
budesonide						0.312
MYVACET 9-45	0.021	0.021	0.001	0.039	0.001	0.039
TWEEN 60	0.142	0.142		0.158		1.171
ethanol	5.642	5.642	0.735	11.00	0.183	11.50
n-butane						
heptafluoropropane	94.053	94.053	99.235	87.216	99.449	86.978

The Examples of above illustrate the preparation of suspension aerosols which are easily redispersed. In order to achieve better homogenisation of the mixtures and to avoid adsorptive effects, the addition of 0.5 - 20 %, especially 0.5 - 12 % ethanol is recommended.

The Claims defining the invention are as follows:

1. A pharmaceutical composition for use as an aerosol comprising:
a) a liquefied propellant gas or propellant gas mixture having a vapour pressure of more than 1 bar and less than 6 bar (20°C) from the group consisting of unsubstituted hydrocarbons and partially to completely fluorinated hydrocarbons;
b) a non-ionic surfactant from the group consisting of monoacetylated or diacetylated monoglycerides;
c) a pharmaceutical active ingredient or active ingredient combination and, optionally,
d) other conventional pharmaceutical excipients that are suitable for aerosol formulations.

2. A pharmaceutical composition according to claim 1 comprising:
a) a propellant gas or propellant gas mixture from the group consisting of propane, n-butane, isobutane, di-, tri-, or tetrafluoroethane and heptafluoropropane;
b) a non-ionic surfactant from the group consisting of monoacetylated monoglycerides;
c) a pharmaceutical active ingredient or active ingredient combination from the group consisting of antiallergics, betasympathomimetics, anticholinergics and corticoids, and, optionally,
d) further conventional pharmaceutical excipients that are suitable for aerosol formulations.

3. A pharmaceutical composition according to claim 1 comprising:
a) a propellant gas or propellant gas mixture from the group consisting of propane, n-butane, isobutane, tetrafluoroethane and heptafluoropropane;
b) a non-ionic surfactant from the group of the monoacetylated monoglycerides;
c) a pharmaceutical active ingredient or active ingredient combination from the group consisting of disodium cromoglycate, salbutamol, salmeterol, formoterol, oxitropium bromide, ipratropium bromide, budesonide, flunisolide, beclomethasone and triamcinolone, and, optionally,
d) further conventional pharmaceutical excipients that are suitable for aerosol formulations.

4. A pharmaceutical composition according to claim 1 comprising:
a) the propellant gas heptafluoropropane;
b) a non-ionic surfactant from the group consisting of monoacetylated monoglycerides;
c) a pharmaceutical active ingredient or active ingredient combination from the group

consisting of disodium cromoglycate, salbutamol, salmeterol formoterol, oxitropiumbromide, ipratropium bromide, budesonide, flunisolide, beclomethasone and triamcinolone and, optionally,
d) further conventional pharmaceutical excipients that are suitable for aerosol formulations.

5. A process for the preparation of the pharmaceutical composition according to claim 1 which comprises placing the pharmaceutical active ingredient or active ingredient combination c) in a pressure-tight vessel and introducing, in any desired sequence of the steps, the non-ionic surfactant b), where appropriate the conventional pharmaceutical excipients d), and introducing the propellant gas or propellant gas mixture a), homogenising, and introducing the homogeneous mixture into dosing vessels suitable for aerosol formulations.

6. A pharmaceutical composition according to claim 1 for use as an aerosol formulation in a therapeutic method of treatment of on the human or animal body.

7. A pharmaceutical composition according to claim 1 for use as an aerosol formulation in nasal or oral inhalation therapy for the treatment of disorders of the respiratory tract.

8. The use of a non-ionic surfactant from the group of the monoacetylated or diacetylated monoglycerides for the preparation of a pharmaceutical composition that can be used as an aerosol formulation.

DATED this 5th day of March, 1992

CIBA-GEIGY AG and
JAGO PHARMA AG
By Their Patent Attorneys
DAVIES COLLISON CAVE

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